Research Paper

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Effects of Buflomedil on Spontaneous Vasomotion and Mean Arteriolar Internal Diameter in the Hamster Cheek Pouch

Key Words
Vasomotion, arteriolar
Arteriolar diameter
Microcirculation
Hamster cheek pouch

Abstract

Intravital microscopy of the hamster cheek pouch microvasculature was used for in vivo studies on the effects of buflomedil, phentolamine (α-adrenergic receptor antagonist) and norepinephrine on the mean internal arteriolar diameter and spontaneous vasomotion. All drugs were applied topically. The vasomotor activity was studied in 125 arterioles (internal diameter range 18.0–62.0 μm) of 34 preparations. Addition of buflomedil (10^{-9} to 10^{-5} *M*) did not affect the arteriolar diameter significantly (from 100.7 ± 3.5 to 106.4 ± 1.8%, values expressed in percent of the initial diameter as mean ± SE), but increased the vasomotion frequency and amplitude by approximately 20% (from 7.5 ± 0.3 to 9.2 ± 0.2 cpm) and 30% (from 7.3 ± 0.3 to 10.0 ± 0.5 μm), respectively. Phentolamine (10^{-9} to 10^{-5} *M*) dose-dependently increased the microvascular diameter (from 102.3 ± 1.2 to 139.1 ± 4.3%) and reduced the vasomotion frequency and amplitude (from 8.0 ± 0.3 to 1.9 ± 0.5 cpm and from 9.0 ± 2.1 to 3.1 ± 0.2 μm, respectively). Addition of buflomedil (10^{-7} *M*) reduced the vasodilation evoked by phentolamine (from 103.3 ± 0.7 to 127.0 ± 1.5%) and potentiated its depressive effect on vasomotion frequency and amplitude (from 7.6 ± 0.1 to 1.0 ± 0.3 cpm and from 9.0 ± 0.3 to 1.9 ± 0.6 μm, respectively). Norepinephrine (10^{-9} to 10^{-5} *M*) dose-dependently decreased to arteriolar diameter (from 102.3 ± 0.7 to 69.6 ± 1.6%) and the vasomotion frequency and amplitude (from 8.4 ± 0.2 to 0.4 ± 0.3 cmp and from 8.7 ± 0.2 to 0.5 ± 0.4 μm, respectively). Addition of buflomedil (10^{-7} *M*) reduced the vasoconstriction elicited by norepinephrine (from 103.2 ± 0.9 to 82.9 ± 3.9%) and restored the vasomotion frequency and amplitude (from 8.4 ± 0.3 to 7.8 ± 0.4 cpm and from 8.6 ± 0.2 to 7.8 ± 0.3 μm, respectively). The effects observed with buflomedil on the hamster cheek pouch microcirculation suggest a direct action on the smooth muscle excitability and further support its properties as a competitive inhibitor of α-adrenergic receptors and as a weak calcium antagonist.

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Introduction

In several tissues, precapillary vessels exhibit spontaneous luminal variations, termed vasomotion. The mechanisms that either cause or control these spontaneous diameter oscillations are still not well known, but it is generally accepted that arteriolar vasomotion plays an important role in capillary flow regulation and fluid exchange.

Buflomedil has been used for the treatment of peripheral vascular disease [1, 2]. Studies by Fagrell and Hermansson [3] have shown that buflomedil is effective in the treatment of patients with acral gangrene, and Trübestein et al. [4] demonstrated an improvement in the claudication distance in patients with chronic arterial disease. Since no significant changes in the systemic hemodynamic parameters could be detected, these effects could be due to an improvement in the (1) rheological properties of the blood [5]; (2) oxygen distribution [6], and/or (3) collateral circulation [7]. Vanhoutte et al. [8], using rings of canine arteries and veins and perfused gracilis muscles, have shown that buflomedil blocks α-adrenergic receptors but that it is not selective for either α_1- or α_2-adrenergic receptor subtype. This inhibitory effect of buflomedil was not affected by endothelial removal but was reduced by chemical sympathectomy with 6-hydroxydopamine and by inhibition of neuronal uptake. In isolated electrically stimulated guinea-pig heart preparations (papillary muscles and atria), buflomedil has shown a weak calcium antagonistic activity and has also produced a dose-dependent negative inotropic effect [9].

The present study was carried out to obtain direct information on the effects of buflomedil on vasomotion. Previous experiments in our laboratory [10] have demonstrated that the hamster cheek pouch is a suitable model for this study. In the preparation, spontaneous arteriolar vasomotion occurs both regularly and in such a way that is readily influenced by various changes in the physical and chemical environment of the preparation [10]. In this study we have explored how vasomotion and the mean arteriolar diameter were affected by buflomedil in the following experimental conditions: (1) control; (2) in combination with different concentrations of an α-adrenergic receptor blocker (phentolamine), and (3) in combination with different concentrations of norepinephrine.

Materials and Methods

Experiments were performed on arterioles of the cheek pouch of 34 male hamsters (*Mesocricetus auratus,* Engle Laboratories, Farmersburg, Ind., USA) weighing 101 ± 3.2 g (mean ± SEM). Anesthesia was induced by an intraperitoneal injection of 0.1–0.2 ml of sodium pentobarbital (Mebumal vet., ACO AB, Sweden, 60 mg/ml) and maintained with α-chloralose [1,2-O-(2,2,2,-trichlorethyliden) α-*D*-glucofuranose, Merck, Darmstadt, Germany; 100 mg/kg] administered through the left femoral vein. The left femoral artery was also cannulated for pressure measurements. Throughout surgery and the subsequent experiment, the temperature of the animals was kept at 37.5 °C by means of a heating pad and a rectal thermistor as a reference for feedback control. A tracheal tube was inserted to facilitate spontaneous breathing.

For the experiments, cheek pouch preparations were dissected according to Duling [11], recently modified by Bouskela and Grampp [10], and mounted in an experimental chamber where they were continuously superfused, at a rate of 4.6 ml/min, with a N-(2-hydroxyethyl)piperazine-N'-2-ethanesulfonic acid (HEPES)-supported HCO_3^--buffered solution (composition in m*M*: NaCl 110.0, KCl 4.7, $CaCl_2$ 2.0, $MgSO_4$ 1.2, $NaHCO_3$ 18.0, HEPES 15.39 and HEPES Na^+-salt 14.61). The temperature of the superfusion solution was kept at 36.5 °C, the pH was set to 7.40 by bubbling the solutions continuously with 5% CO_2 and 95% N_2. Throughout the experiments, the same gas mixture was also gently blown over the experimental chamber in order to keep the level of pO_2, measured with an oxygen electrode, at 12–15 mm Hg in the superfusion solution.

Solutions containing drugs (arterenol hydrochloride, Sigma Chemical, St. Louis, Mo., USA; buflomedil hydrochloride, Laboratoire L. Lafon, Maisons-Alfort, France; papaverine, Kabi Pharmacia, Uppsala, Sweden; phentolamine, Sigma Chemical, St. Louis, Mo., USA) were freshly prepared for each experiment.

The animals were divided into 5 groups. Group I, 10 animals used to study the effects of buflomedil alone; group II, 6 animals used to study the effects of phentolamine alone; group III, 6 animals used to study the effects of the combination phentolamine + buflomedil; group IV, 6 animals used to study the effects of norepinephrine alone, and group V, 6 animals used to study the effects of the combination norpinephrine + buflomedil.

For microcirculatory measurements, the preparations were placed under an intravital videomicroscope (optical magnification 300, with an objective Nikon M Plan SLWD 20X NA 0.35) where they were allowed to rest for 30 min at 36.5 °C. If after this time there was: (a) an indication of a good vascular tonus (which implied that the arteriolar internal diameter could increase by 56 ± 3% through topical application of papaverine, 10 μg/ml, at the end of each experiment); (b) a brisk blood flow in all parts of the preparation including the large veins (where individual erythrocytes should not be discerned in the image of the blood stream), and (c) no tendency for leukocytes to adhere to the venular walls, experiments were performed by taking 3-min videotape recordings of each 3–6 selected arterioles per preparation, both in initial control conditions (3 measurements) and, subsequently, 10–15 min after each experimental intervention. Each drug was applied for 60–80 min before the highest concentration was given. The arterioles were selected based on the facility to return to them, at the same site, repeatedly throughout the experiment.

From the videotape recordings, continuous registrations of the internal diameter of selected arterioles were obtained by means of an image shearing device (IPM, model 907). Time averages of the vessel diameter and, if vasomotion was present, of its frequency and amplitude could then be inferred from the whole length of each diameter registration (3 min in each case). If present, vasomotion normally causes the vessel diameter to oscillate quite symmetrically around a stable average value. The latter could therefore be assessed by simply

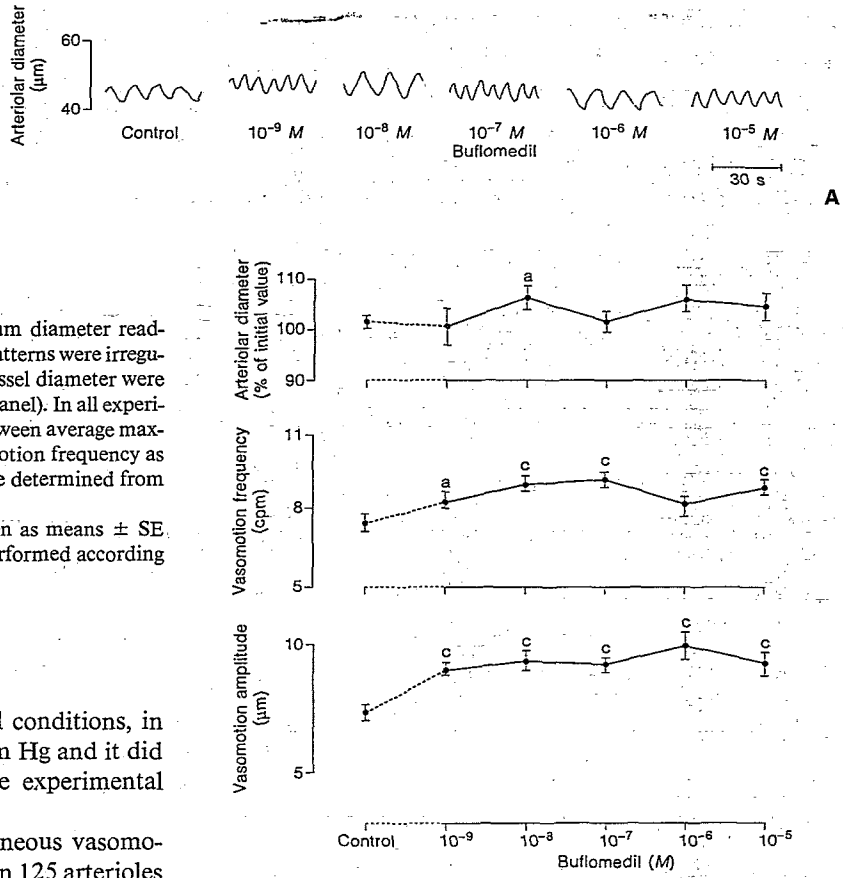

Fig. 1. A Diameter recordings on 1 arteriole under control conditions and after addition of different concentrations of buflomedil to the superfusion solution, as indicated. **B** Relationships between the concentration of buflomedil added to the superfusion solution and the diameter and vasomotion properties in 30 arterioles from 10 different preparations. First panel: relationship between drug concentration and arteriolar diameter. Diameter values are given as fractions of normalized (100%) control readings taken at the beginning of each experiment. Second and third panels: relationships between drug concentration and vasomotion frequency and amplitude. Significantly different from control values in absence of buflomedil: [a] at the 5% level, and [c] at the 0.1% level. All recordings were made 10–15 min after each increase in buflomedil concentration.

computing the means of maximum and minimum diameter readings. Only in a few experiments, the vasomotion patterns were irregular, and in these cases estimates of the average vessel diameter were obtained by graphical means (as in fig. 2A, lower panel). In all experiments, the vasomotion amplitude was defined between average maximal and minimal vessel diameter and the vasomotion frequency as the inverse of the average cycle length, as could be determined from each diameter registration.

In statistical presentations, estimates are given as means ± SE unless otherwise noted. Significance tests were performed according to the Student's t test method.

Results

The mean arterial pressure, in control conditions, in the 5 groups studied, was 102.3 ± 1.8 mm Hg and it did not change significantly with any of the experimental interventions.

The internal diameter and the spontaneous vasomotion were measured in control conditions in 125 arterioles (internal diameter range 18.0–62.0 µm; 37.7 ± 1.9 µm) of 34 preparations. We noticed a small variation in the arteriolar internal diameter during the control period which did not elicit any change in vasomotion frequency and amplitude. Due to this fat, the arteriolar internal diameter has been normalized to its initial value observed after the 30-min resting period while the vasomotion frequency (range 3–11 cpm; 7.7 ± 0.1 cpm) and amplitude (range 4.0–15.0 µm; 8.3 ± 0.2 µm) are shown for the whole control period. No systematic difference between the various control groups could be detected.

Buflomedil

WEF97Buflomedil, applied topically after the control period in concentrations from 10^{-9} to 10^{-5} *M*, did not affect the internal arteriolar diameter significantly (from 101.7 ± 0.8 to 106.4 ± 2.7%), but it increased the spontaneous vasomotion frequency by approximately 20% (from 7.5 ± 0.3 to 9.2 ± 0.2 cpm) and its amplitude by approximately 30% (from 7.3 ± 0.3 to 10.0 ± 0.5 µm). The results obtained in 10 different cheek pouch preparations and 30 arterioles (internal diameter range 18.0:53.0 µm; 37.9 ± 1.2 µm) are shown in figure 1. In all cases, it was found that the effects of buflomedil were completely reversed by returning the preparations to control conditions.

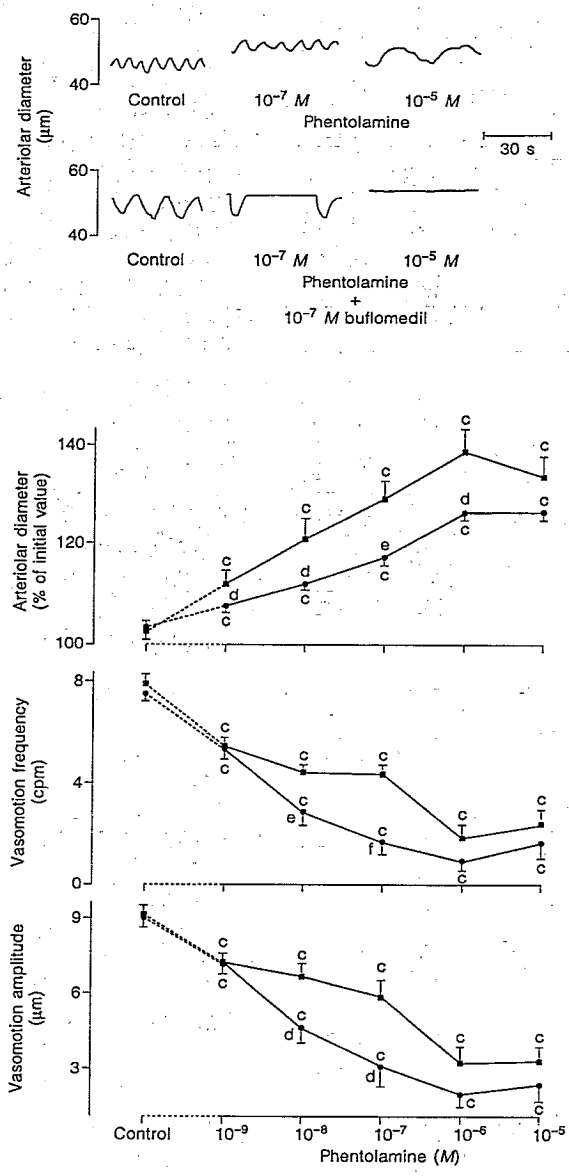

Fig. 2. A Diameter recordings on 2 arterioles under control conditions and after addition of different concentrations of phentolamine (top panel) or phentolamine + 10^{-7} *M* buflomedil (bottom panel) to the superfusion solution, as indicated. **B** Relationships between different concentrations of phentolamine combined (●) or not (■) with 10^{-7} *M* buflomedil added to the superfusion solution and diameter and vasomotion properties in 20 arterioles (phentolamine curve) from 6 different preparations or 25 arterioles (phentolamine + buflomedil curve) also from 6 different preparations. First panel: relationshbip between phentolamine and phentolamine + buflomedil and arteriolar diameter. Diameter values are given as fractions of normalized (100%) control readings taken at the beginning of each experiment. Second and third panels: relationships between phentolamine and phentolamine + buflomedil and vasomotion frequency and amplitufe. Signficantly different from control values in absence of drugs: and ^{c} at the 0.1% level. Significantly different from the phentolamine value: ^{d} at the 5% level; ^{e} at the 1% level, and ^{f} at the 0.1% level. All recordings were made 10–15 min after each change in the superfusion solution.

α-Adrenergic Receptor Blockade

Phentolamine (α-adrenergic receptor blocker), applied topically, dose-dependently (10^{-9} to 10^{-5} *M*) increased the mean internal arteriolar diameter (range 18.0–48.0 μm; 34.8 ± 1.7 μm) and decreased vasomotion frequency and amplitude (from 8.0 ± 0.3 to 1.9 ± 0.5 cpm and from 9.0 ± 2.1 to 3.1 ± 0.2 μm, respectively). When 10^{-6} and 10^{-5} *M* of phentolamine were added to the superfusion solution, 10 and 7 of the 20 arterioles studied did not show detectable cyclic changes in the internal diameter, respectively. In these cases, we have assumed that the vasomotion frequency and amplitude were equal to zero. Addition of buflomedil (10^{-7} *M*) to the superfusion solution, reduced the arteriolar (internal diameter range 18.0–48.0 μm; 32.0 ± 1.3 μm) vasodilatation evoked by phentolamine (from 103.3 ± 0.7 to 127.0 ± 1.5%) and potentiated its depressive effect on vasomotion frequency and amplitude (from 7.6 ± 0.1 to 1.0 ± 0.3 cpm and from 9.0 ± 0.3 to 1.9 ± 0.6 μm, respectively) in the concentration range 10^{-9} to 10^{-7} *M*. When 10^{-8}, 10^{-7}, 10^{-6} and 10^{-5} *M* of phentolamine combined with 10^{-7} *M* of buflomedil were added to the superfusion solution, 7, 13, 16 and 16 of the 25 arterioles studied did not show detectable cyclic changes in the internal diameter, respectively. Again, in these cases, we have assumed that the vasomotion frequency and amplitude were equal to zero. Moreover, when 10^{-7} *M* phentolamine + 10^{-7} *M* buflomedil were added, 5 of the 25 arterioles studied showed a diameter registration similar to the one showed in figure 2A, lower panel, i.e., a period of suppressed vasomotion activity without any increase in cycle length. The results obtained are shown in figure 2. In these experiments, the effects of phentolamine and the combination phentolamine + buflomedil were not completely reversed by returning the preparations to control conditions (the standard washout period was 30 min).

Norepinephrine

Norepinephrine (10^{-9} to 10^{-5} *M*), applied topically, dose-dependently decreased the arteriolar internal diameter (range 18.0–60.0 µm; 35.0 ± 2.0 µm) and the spontaneous vasomotion frequency and amplitude (from 8.4 ± 0.2 to 0.4 ± 0.3 cpm and from 8.7 ± 0.2 to 0.5 ± 0.4 µm, respectively). When 10^{-7}, 10^{-6} and 10^{-5} *M* of norepinephrine were added to the superfusion solution, 3, 23 and 21 of the 25 studied arterioles studied did not show detectable cyclic changes in the internal diameter, respectively. In these cases, we assumed that the vasomotion frequency and amplitude were equal to zero. Addition of buflomedil (10^{-7} *M*) to the superfusion solution reduced the elicited arteriolar (internal diameter range 18.0–62.0 µm; 37.8 ± 2.5 µm) vasoconstriction (from 103.2 ± 0.9 to 82.9 ± 3.9%) and restored the vasomotion frequency and amplitude (from 8.4 ± 0.3 to 7.8 ± 0.4 cpm and from 8.6 ± 0.2 to 7.8 ± 0.3 µm, respectively). The results obtained are shown in figure 3. In all cases, it was found that the effects of norepinephrine and the combination norpinephrine + buflomedil were completely reversed by returning the preparations to control conditions.

Discussion

The main findings of the present investigation were that: (1) buflomedil applied topically after the control period did not affect the arteriolar diameter significantly but increased vasomotion frequency and amplitude by approximately 20 and 30%, respectively; (2) phentol-

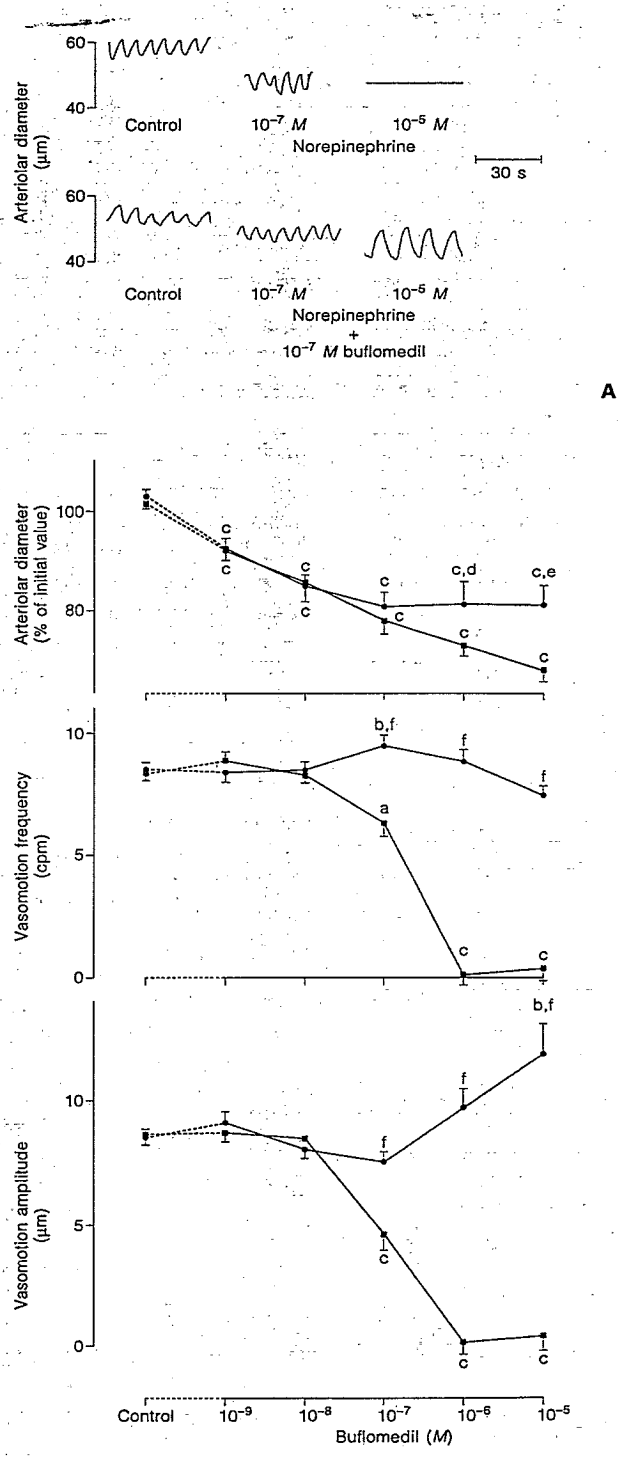

Fig. 3. A Diameter recordings on 2 arterioles under control conditions and after addition of different concentrations of norepinephrine (top panel) or norepinephrine + 10^{-7} *M* buflomedil (bottom panel) to the superfusion solution, as indicated. **B** Relationships between different concentrations of norepinephrine combined (●) or not (■) with 10^{-7} *M* buflomedil added to the superfusion solution and diameter and vasomotion properties in 25 arterioles from 6 different preparations (each curve). First panel: relationship between norepinephrine and norepinephrine + buflomedil concentration and arteriolar diameter. Diameter values are given as fractions of normalized (100%) control readings taken at the beginning of each experiment. Second and third panels: relationships between norepinephrine and norepinephrine + buflomedil and vasomotion frequency and amplitude. Significantly different from control in absence of any drug. [a] at the 5% level; [b] at the 1% level, and [c] at the 0.1% level. Significantly different from norepinephrine value: [d] at the 5% level; [e] at the 1% level, and [f] at the 0.1% level. All recordings were made 10–15 min after each change in the superfusion solution.

amine (α-adrenergic receptor blocker) dose-dependently increased the microvascular diameter and reduced vasomotion frequency and amplitude; (3) addition of buflomedil reduced the vasodilation evoked by phentolamine and potentiated its depressive effect on vasomotion frequency and amplitude; (4) norepinephrine dose-dependently decreased the arteriolar diameter and the vasomotion frequency and amplitude, and (5) addition of buflomedil reduced the vasoconstriction elicited by norepinephrine and restored the vasomotion frequency and amplitude.

The arteriolar vasomotion in the hamster cheek pouch is quite comparable in frequency and amplitude to that observed in other connective tissues, such as the bat wing [12] or the cat mesentery [13]. However, it appears to have a lower frequency than the vasomotor activity seen in skeletal muscle, such as the rabbit tenuissimus muscle (5–32 cpm) [14, 15], bat coracocutaneous muscle (24–75 cpm) [16] and the rat cremaster muscle (25–35 cpm) [17].

Characteristically, in the hamster cheek pouch the frequency and amplitude of the arteriolar vasomotion show no distinct correlation to the vessel diameter (in a relatively narrow diameter range, corresponding to A_2 and A_3 arterioles). This is in general agreement with what has been found to be true for arteriolar vasomotion in both connective tissue [12] and skeletal muscle [17]. One implication of this lack of clear correlation between vessel size and vasomotion might be that the mechanisms underlying vasomotion are of a uniform type in the range of vessel diameters investigated and that force production (number of muscle elements) grows approximately in proportion with the vessel wall tension according to Laplace's law. However, Colantuoni et al. [18] found that, in the hamster skin fold preparation, the vasomotion frequency decreased from a maximum of 9–15 cpm in 8- to 15-μm A_4 arterioles to 1–3 cpm in 70- to 100-μm A_1 small arteries. This discrepancy could be due to the fact that, in the hamster cheek pouch preparation, there is a consistent lack of synchrony in vasomotor movements in related mother and daughter arterioles in the vessels studied. Similar conditions were also observed in the vascular bed of the bat wing, where the different segments of the arteriolar tree appear to move quite independently [12]. It seems reasonable to assume that in these cases different vessel segments are equipped with their own pacemaker centers and that, in particular, the current conductivity between neighboring muscle cells is reduced in the vicinity of vessel branchings.

In this study, no distinct correlation was found between the frequency and amplitude of the vasomotor activity. The same was also observed in the bat wing [12] but not in the hamster skin fold, where there is a positive correlation between vasomotion frequency and relative amplitude [18], nor in the rabbit tenuissimus muscle, where the two parameters are correlated in a negative way [15]. Why there are such differences in vasomotor properties is unclear. However, it might be assumed for the hamster cheek pouch that the lack of correlation between vasomotion frequency and amplitude has to do with the various pacemaker centers in different parts of the vascular tree, which function independently (see above) and differ from each other more with respect to rate than to the amount of their pacemaker current production.

Addition of buflomedil to the superfusion solution after the control period increased vasomotion frequency and amplitude by 20 and 30%, respectively (fig. 1), without any significant changes in the mean arteriolar internal diameter. Spontaneous arteriolar vasomotion most likely originates from the intrinsic ability of vascular smooth muscle cells to depolarize spontaneously, Ca^{2+} ions thus being mobilized and initiating contraction. Combining the stretch sensitivity and the spiral disposition of vascular smooth muscle cells in contracting arterioles, the vasomotion wave may be transmitted mechanically by locally generated potentials, superimposed on the pacemaker-like activity and transmitted through the gap junctions [19, 20]. In addition, α- and β-adrenergic receptor-mediated processes, as facilitating or damping mechanisms, respectively, may modulate the frequency and amplitude of the arteriolar vasomotion to some extent [21]. It is conceivable to assume that buflomedil, with properties as a competitive inhibitor of α-adrenergic receptors and weak Ca^{2+} antagonist, could have an effect on the smooth muscle membrane excitability.

Phentolamine, an α-adrenergic receptor blocker, applied topically, dose-dependently increased the mean arteriolar internal diameter and reduced the vasomotion frequency and amplitude (fig. 2), probably due to the vasodilation itself [10]. Similar findings have been reported in the hamster skin fold preparation by Colantuoni et al. [21]. Addition of buflomedil reduced the vasodilation evoked by phentolamine possibly due to its competitive inhibition of α-adrenergic receptors [22] and potentiated its depressive effect on vasomotion frequency and amplitude (fig. 2), in the concentration range 10^{-9} to 10^{-7} M of phentolamine, possibly due to its calcium antagonist properties. Our results do not agree with the work reported by Intaglietta et al. [23] and the possible

reasons for the discrepancy might be that (1) vasomotion was present in 62% of the arterioles smaller than 25 μm and in 45% of the arterioles bigger than 25 μm in the reported unanesthetized preparation (hamster skin fold) while in our preparation (hamster cheek pouch), under α-chloralose anesthesia, vasomotion was present in all visible arterioles with internal diameter between 18.0 and 72.0 μm, and (2) the drugs used in the hamster skin fold preparation [23], pentobarbital and phentolamine, were given systemically and elicited a decrease in the mean arterial pressure of the animal. The fact that vasomotion restarted after the injection of buflomedil in the hamster skin fold preparation could be due to the observed recovery in arterial pressure and not a direct effect of buflomedil. In our preparation (hamster cheek pouch), the drugs were applied topically and no significant changes in mean arterial pressure could be detected by the addition of buflomedil. In fact several reports in the literature demonstrate the influence of mean arterial pressure or transmural pressure on the spontaneous arteriolar vasomotion. In the mesentery, during reduction in perfusion pressure, spontaneous vasomotion declined and finally ceased [24] or decreased in frequency with a concomitant increase in amplitude [13]. In the rabbit tenuissimus muscle, a gradual reduction in arterial pressure resulted in either an abrupt disappearance of vasomotion in transverse arterioles [15], in periods of regular vasomotion in the terminal arterioles, intercalated with periods of no vasoactivity which became longer when pressure was reduced [14], or in a gradual decrease in vasomotion frequency concomitant with an increase in vasomotion amplitude [25]. In the bat wing, changes in transmural pressure resulted in a progressive decrease in rhythmic vasomotion frequency and amplitude [12]. In the rat cerebral microcirculation, during stepwise pressure reduction, the vasomotion frequency decreased progressively while its amplitude showed a reversed U-shaped curve with a peak at 60–80 mm Hg [26]. In our study, all drugs were applied topically to avoid the influence of systemic effects.

Norepinephrine, applied topically, dose-dependently decreased the arteriolar internal diameter and vasomotion frequency and amplitude, probably due to the vasoconstriction itself. Although sympathetic nervous system activity largely contributes to the control of normal cardiovascular functions, epinephrine and norepinephrine can initiate an exaggerated inward flux of Ca^{2+} ions into vacular smooth muscle cells, inducing a sustained constriction of resistance vessels [27]; as such, norepinephrine- or epinephrine-induced constrictions of arterioles represent, to some extent, a model for excessive Ca^{2+} influx in vascular smooth muscle cells. The reduction in the arteriolar vasoconstrictor responses and the restoration of vasomotion observed when buflomedil was added to the superfusion solution containing norepinephrine, in the hamster cheek pouch preparation in vivo, in the concentration range 10^{-7} to 10^{-5} *M*, further supports the inhibitory action of this compound on calcium channels. It should be mentioned that the calcium influx induced by norepinephrine is mainly through receptor-operated channels while calcium channel blockers usually act on voltage-operated channels. The pool of calcium available in the cytoplasm, however, results from the conductivity of all calcium channels operating in the smooth muscle cell membrane. Calcium ions play a pivotal role in the regulation of various cellular processes, including those bearing on vascular smooth muscle tone [28].

In the hamster skin fold preparation, systemic injection of norepinephrine increased the frequency of vasomotion and reduced mean diameter at low dosage [21]. The observed discrepancy could be due to the effects on mean arterial pressure elicited by the systemic injection of this vasoactive substance.

In conclusion, the effects observed with buflomedil on the hamster cheek pouch microcirculation in vivo could be explained by its competitive inhibition of α-adrenergic receptors and weak calcium antagonist properties. It is also possible that the increased erythrocyte deformability, inhibition of platelet aggregation and decrease in blood viscosity elicited by buflomedil play a role. However, the combination of buflomedil with a pure α- and β-adrenergic receptor agonists, α_1- and α_2-adrenergic receptor antagonists and calcium blockers should be investigated in order to clarify its mechanisms of action in the microcirculation, especially on the spontaneous arteriolar vasomotion.

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